REMARKS

Status of the Application

At the time the Office Action was mailed, claims 1, 2, 4-6 and 14-22 were pending in the application. All were rejected under 35 U.S.C. 103 for the reasons previously set forth in Paper No. 20, Section 4, pages 2-7 and in Section 5, pages 7-11. Additionally, claims 18-22 were newly rejected under 35 U.S.C. 103 for the same reasons further in view of Sashira (Med. J. Kagoshima Univ, 1986, 38:15-48); and all of the pending claims were newly rejected for failing to meet the written description requirement of 35 USC 112, first paragraph. No claims were allowed.

Upon entry of this amendment, claims 1 and 18 will have been amended, and no claims will have been added or cancelled. Therefore, claims 1, 2, 4-6 and 14-22 as amended will be before the examiner for consideration.

Maintained Rejection Under U.S.C. § 103

Claims 1, 2, 4-6 and 14-22 were rejected under 35 U.S.C. 103 for the reasons previously set forth in the office action of November 6, 2001 (Paper No. 20, Section 4, pages 2-7 and Section 5, pages 7-11).

As to the section 5 rejection, the Office Action indicated that the declaration under 37 CFR 1.132 filed February 1, 2002 to remove Debinski et al., Abstract, 17th International Cancer Congress, Rio de Janeiro, 1998 (the "Abstract") as a prior art reference was acknowledged and entered. It did not, however, state that this declaration removed the Abstract as a prior art reference. Moreover, this reference was apparently not removed as a prior art reference because

the Office Action maintained the rejection under section 5 (which relied on the "Abstract."). This issue was raised in a May 24, 2002 telephonic interview between applicant's attorney and Examiner Ungar. As indicated in the interview summary mailed June 17, 2002 (Paper No. 25), the examiner reiterated that the section 5 rejection remained. Because the section 5 rejection relied on the Abstract as a prior art reference, and the declaration under 37 CFR 1.132 filed February 1, 2002 was entered, the maintenance of this rejection is believed to be in error as absent the Abstract, the section 5 rejection would be identical to the section 4 rejection (which did not rely on the Abstract). Applicants respectfully request (1) a statement as to whether the Abstract was removed as a prior art reference by the declaration under 37 CFR 1.132 filed February 1, 2002 and (2) withdrawal of this rejection because it would be identical to the section 4 rejection absent the availability of the Abstract as a prior art reference.

The section 4 rejection was made by combining three references, namely: US Patent No. 5,614,191 (the "191 patent"); Debinski et al. (JBC, 1996, 271:22428-22433; the "Debinski Paper"); and BioCentury Extra (1996, 465:1; the "BioCentury Article"). The Abstract was cited as evidence to support the rejection, although the Office Action made clear that it was not relied upon. This rejection is improper because the examiner has not met the burden for making out a prima facie case of obviousness.

As previously indicated, the invention relates to the development of methods for reducing the growth rate of glioma cells in a mammalian subject by either (1) delivering into the subject a molecule having an IL13 moiety and a cytotoxic moiety or (2) contacting glioma cells within the cranium of the subject with such a molecule. The invention was facilitated by applicants' discovery that IL13 receptors are expressed on glioma cells in vivo/in situ. Based on this discovery, cytotoxic molecules were directed to the IL13 receptors expressed by glioma cells to

reduce their growth rate. As described in the specification, this method was shown to successfully treat animals bearing either subcutaneous or intracranial glioma tumors.

Neither the '191 patent, the Debinski Paper, or the BioCentury Article teach anything about IL13R expression in vivo or in situ. The '191 patent does not describe any in vivo or in situ results. Rather, it presents in vitro data relating to renal, colon, skin, and stomach cancer cell lines. It does not mention "glioma" or "brain." The Debinski Paper also does not describe any in vivo or in situ results. Instead, it discloses that established glioma cell lines and primary cultures of glioblastoma multiforme cells are sensitive to hIL13-based toxins in in vitro assays. The BioCentury Article does describe in vivo results. These, however, relate to the use of a carmustine-containing polyanhydride wafer for implant into the brain of patients with glioblastoma multiforme. It is entirely silent with respect to IL13.

In maintaining the rejection, the Office Action argued that:

> ...it would have been obvious, and one of ordinary skill in the art would have expected to and have been motivated to treat glioma cells, in vivo with the known product, given what was known in the art and the clear teaching that the primary explant cells overexpressed the receptor.

Among the requirements for making out a prima facie case of obviousness, the examiner has the burden of proving at least two things. First, that the prior art relied on, coupled with the knowledge generally available in the art at the time of the invention, provided the skilled artisan some motivation or incentive to modify a reference to arrive at the claimed invention (In re fine, 837 F.2d 1071, 1074 (Fed. Cir., 1988); In re Skinner, 2 USPQ2d 1788, 1790 (Bd. Pat. App. & Int., 1986)). Second, that the proposed modification must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. See Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1209 (Fed. Cir. 1991).

To arrive at the subject matter of claims 1 and 18 (from which the remainder of the claims ultimately depend) from what was taught in the combination of references cited, the skilled artisan might have tried to administer IL13 receptor-targeting cytotoxins to animal subjects having a glioma tumor in the hope that this procedure would have been successful in killing or reducing the growth rate of the tumor cells. Even if it could be argued that the combined references suggest or provide motivation to try this, a prima facie case of obviousness has not been made because the second requirement has clearly not been met because there was no reasonable certainty that the attempt to treat a glioma in a subject by this method would have succeeded. See In re O'Farrell, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (Being "obvious to try," is not the standard under 35 USC 103).

Supporting this, it is common knowledge that a great many putative compounds for treating cancer have failed even though they were successful in killing tumor cells in in vitro assays. Such in vitro assays are employed as merely a screening tool to sort out those compounds having potential chemotherapeutic value from those that do not. To actually show that such potentially useful compounds have an anti-cancer effect in vivo, animal experiments must be performed. Those compounds effective in in vitro assays often fail in the animal models because animal models are much more complicated. For example, the microenvironment of a solid tumor in an animal is vastly different from a suspension of cells in an in vitro culture (e.g., cells in the center of a solid tumor may not be accessible to a chemotherapeutic agent; and cells of a solid tumor interact with non-tumor cells as well as with hormones, chemokines, cytokines, etc. that are not likely the same as those in in vitro cultures). As another example, potential chemotherapeutic compounds are much more likely to be metabolized in an animal than in a culture of cells. Further, in animals but not cell cultures, the immune system may interfere with

the action of the compound.

The Office Action argued that because in vitro cultures of glioma cells explanted from subjects brains were shown to express IL13 receptors and be killed by IL13 receptor-targeting cytotoxins, that the skilled artisan at the time the invention was made would have had a reasonable expectation that administering such cytotoxins to animals having glioma tumors would have succeeded in killing or reducing the growth rate of cells comprising the tumor. Applicants dispute this for two reasons. First, the in vitro data of the Debinski Paper was obtained using cultured cells- not biopsy samples. Second, even if cultured glioma cells could be equated with glioma cells in situ, at the time the invention was made, it was far from certain that administering IL13 receptor-targeting cytotoxins would kill or reduce the growth rate of glioma tumor cells in situ.

In the Office Action, in response to applicants' previous arguments, the examiner maintained the position that because the primary glioblastoma cell cultures described in the Debinski Paper expressed IL13 receptors and were sensitive to IL13 receptor-targeting cytotoxins, similar results would have been expected to be obtained with glioma cells in tumors in an animal. Although no factual evidence was provided to support this conclusion, applicants, in any case, answered this argument by providing evidence that cultured glioma cells differ from their counterparts in animals in cell surface receptor expression. In the Office Action, the examiner indicated that this evidence was not persuasive because the cultured cells described were from long term cultures rather than short term cultures.

The examiner bears the initial burden of factually supporting any prima facie conclusion of obviousness. See MPEP 2142. Nowhere in the prosecution history of this application has the examiner provided factual support for the proposition that glioma cells in situ express the

same type and level of receptors as do cultured glioma cells. Applicants, on the other hand, have provided evidence that cultured glioma cells do differ significantly from glioma cells in situ. Although, the examiner has attempted to distinguish this evidence from what is described in the Debinski Paper, the examiner still has not supported her findings with any facts.

For example, applicants' February 20, 2002 amendment stated:

> The [November 6, 2001] Office Action addressed this argument by stating:
>
> > The argument has been considered but has not been found persuasive because it is clear from Debinski et al, 1996, that the explant cells do not lose expression of the hIL13R antigen and that the antigen is expressed at a concentration ten times more than that found in the cell lines (see p. 22433, col 1, last paragraph). Contrary to Applicant's arguments, given the extensive overexpression of the receptor in the tumor explant, it would be expected that the antigen would be extensively overexpressed *in situ* and one would have expected to successfully treat a mammal with the method of the combined references. Finally, given the Debinski et al 1998 [the Abstract] findings, it is clear that overexpression of the receptor *in situ* is an inherent property of the receptor on GBM.
>
> Applicants believe this statement relies on inappropriate hindsight-fashioned logic in concluding the crucial point that " ...explant cells do not lose expression of the hIL13R antigen...." In making this statement, the [November 6, 2001] Office Action has assumed that glioma cells in situ/in vivo express the same or more of this antigen. The evidence for making this assumption, however, is not provided by any of the references used to arrive at the rejection. Implicitly recognizing this lack of evidence, the [November 6, 2001] Office Action refers to (but does not rely on) the Abstract [presumably removed by the filed declarations] in support of its argument.

The present Office Action did not address this point, and did not provide any factual support for the conclusion that receptor expression on cultured explanted glioma cells is indicative of receptor expression on glioma cells in situ. Rather, the Office Action appears to skirt this issue, by focusing only on distinguishing the Debinski Paper's cultured glioma cells from glioma cells in long term cultures. Regardless of the merit of this argument, the examiner

still has not introduced any factual evidence supporting her allegation that the claimed invention is prima facie obvious. Accordingly, because the examiner has not met her burden of factually supporting her position, no prima facie case of obviousness has been made.

Furthermore, the Office Action acknowledged but did not respond to applicants argument that the "explant cells" described by the Debinski Paper were not simply cells that were removed from a patient and immediately tested for IL13 receptor expression, but rather were cells treated to several processing steps and then cultured in an RMPI1640-based medium in a humidified incubator. To elaborate on this, in the first column of page 22429, the Debinski Paper indicates that after excision, human surgical glioma specimens were treated with a medium containing various digestive enzymes with constant shaking for 45 minutes to create a cell suspension. This was then passed through gauze and washed in two different salt solutions, subjected to density gradient centrifugation, washed, and finally suspended in a medium containing fetal bovine (not non-fetal human) serum. The cells were cultured in an incubator in the latter medium for at least several hours (even up to 76 hours) before results were obtained. Thus the cultures of "glioma explant cells" were subjected to several treatments that glioma cells in situ would not be exposed to.

As an additional point, even if facts were provided to suggest that receptor expression on cultured glioma cells was indicative of receptor expression on glioma cells in situ, at the invention was made, it was far from certain that administering IL13 receptor-targeting cytotoxins would kill or reduce the growth rate of glioma tumor cells in situ. As discussed above, many agents that exert an anti-cancer effect in vitro, do not do so in animals. In addition to this, it is well known that chemotherapeutic drugs are not fungible commodities that can be used to

successfully treat any and all cancer therapies. Even if one particular drug has been proven to successfully treat a particular type of cancer, this does not mean that the drug is certain or even reasonably likely to be beneficial for treating another cancer type. Notably, although there are a large number of FDA-approved drugs for treating cancer, most are not marketed for treating gliomas in human patients.

In view of the foregoing, because a prima facie case of obviousness has not been made out for the section 4 rejection and because the section 5 rejection is improper (or identical to the section 4 rejection), entry of the amendment and allowance of the claims is respectfully requested.

New Rejection Under U.S.C. § 103

In the Office Action, claims 18-22 were rejected under 35 U.S.C. 103 for the reasons set forth above further in view of Sashira (Med. J. Kagoshima Univ. 1986, 38, 15-48; hereinafter "Sashira"). The Sashira reference was alleged to teach intratumoral administration of drugs for the treatment of brain tumor by-passes. This reference was apparently added for the disclosure of contacting a tumor cell contained within the cranium of a mammalian subject with an anti-tumor agent. Even with the addition of Sashira to the combination of the '191 Patent, the Debinski Paper, and the BioCentury Article, the claimed invention cannot be considered prima facie obvious because, as described above, at the time the invention was made, (1) receptor expression in cultured cells was not shown to correspond to receptor expression in cell in situ and (2) it was far from certain that administering IL13 receptor-targeting cytotoxins would kill or reduce the growth rate of glioma tumor cells in situ

Rejections Under U.S.C. § 112 First Paragraph

Claims 1, 2, 4-6 and 14-22 were newly rejected under 35 U.S.C. 112, first paragraph. The Office Action alleged that the specification "...does not contain a written description of the claimed invention." More specifically, the Office Action stated:

> The limitation of a receptor that binds IL13 with a greater affinity than it binds IL4 recited in claims 1 and 18 has no clear support in the specification and the claims as originally filed. A review of the specification did not reveal support for the newly added limitation.

Although applicants respectfully disagree with this rejection (see, for example, p. 16, lines 16-30 of the specification), in an effort to expedite prosecution of the application, claims 1 and 18 (from which the remainder of the pending claims depend) have been amended to remove recitation of the phrase at issue. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 18-22 were also rejected under 35 U.S.C. 112, first paragraph for allegedly not containing a written description of the claimed invention. Specifically, the Office Action indicated that, in claim 18, the phrase "contacting the glioma cell contained within the cranium of the mammalian subject" has no clear support in the specification or the claims as originally filed. The Office Action further indicated that, after reviewing the specification, the examiner could not find support for this phrase.

The Office Action provided no further explanation of this rejection. Applicants thus assume the rejection was either (1) formal in nature, e.g., because the phraseology was not used in the originally filed application or (2) substantive in nature, e.g., because the examiner could not find within the specification a description of an experiment involving intratumoral injection

of a tumor within the cranium of a mammalian subject.

In response to point (1), such a rejection would be improper because the written description requirement of 35 USC 112 first paragraph contains no in haec verba requirement (see MPEP 2163), and because it is clear that intratumoral injection of a glioma tumor in a mammalian subject inherently results in the step of "...contacting the glioma cell contained within the cranium of the mammalian subject." See following paragraph regarding experiments describing intratumoral injection into a cranium.

As to point (2), applicants direct the examiner to page 21 (also Fig. 4) of the specification, particularly to lines 6-7 (stating "...*scid* mice with established intracranial (i.c.) xenografts of U-251 MG [a human malignant glioma]...") and lines 22-26 (stating "two i.t. [intratumoral] injections of 0.2 ug per mouse of hIL13 CTX in the intracranial model of human glioma (U251 MG) ..."). The phrase "contacting the glioma cell contained within the cranium of the mammalian subject" is thus clearly supported in the specification as originally filed.

Because this rejection in improper in either case, applicants request that it be withdrawn. In the case that applicants have misunderstood this rejection, further elaboration as its basis is requested.

Conclusion

The currently pending claims are supported throughout the specification and are patentable over the prior art. No new matter has been added. This application is now in full condition for allowance, and such action is respectfully requested. A petition for a retroactive extension of time for one month accompanies this response. The Commissioner is hereby

authorized to charge any underpayment or credit any overpayment of fees under 37 CFR 1.16 or 1.17 as required by this paper to Deposit Account 50-0951.

The Examiner is cordially invited to call the undersigned if clarification is needed on any matter within this amendment, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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APPENDIX A

CLEAN COPY OF PENDING CLAIMS

1. (Twice Amended) A method of reducing the rate of growth of glioma cells in vivo in a mammalian subject, the method comprising the step of: delivering into the subject a molecule having an IL13-moiety and a cytotoxic moiety in an amount effective to reduce the rate of growth of the glioma cells.

2. (Amended) The method of claim 1, wherein the glioma cells are glioblastoma multiforme cells.

4. (Amended) The method of claim 1, wherein the glioma cells form a tumor in the mammalian subject and the growth of the tumor is inhibited.

5. (Amended) The method of claim 4, wherein the tumor volume is reduced.

6. (Amended) The method of claim 4, wherein the molecule is delivered by intratumoral injection.

14. The method of claim 4, wherein the tumor is located in the cranium of the mammalian subject.

15. The method of claim 14, wherein the IL13-moiety is hIL13.

16. The method of claim 14, wherein the cytotoxic moiety is a Diphtheria toxin.

17. The method of claim 14, wherein the cytotoxic moiety is a Pseudomonas toxin.

18. (Amended) A method of killing a glioma cell in situ, the method comprising the steps of:

(a) providing a mammalian subject having a cranium containing a glioma cell;
(b) providing a molecule having an IL13-moiety and a cytotoxic moiety; and
(c) contacting the glioma cell contained within the cranium of the mammalian subject with the molecule in an amount effective to kill the glioma cell.

19. The method of claim 18, wherein the glioma cell is a glioblastoma multiforme cell.

20. The method of claim 18, wherein the IL13-moiety is hIL13.

21. The method of claim 18, wherein the cytotoxic moiety is a Diphtheria toxin.

22. The method of claim 18, wherein the cytotoxic moiety is a Pseudomonas toxin.

APPENDIX B

MARKED-UP VERSION OF CLAIMS SHOWING AMENDMENTS MADE

1. (Twice Amended) A method of reducing the rate of growth of glioma cells in vivo in a mammalian subject [, the glioma cells comprising an IL13-specific receptor that specifically binds IL13 with a greater affinity than it binds IL4], the method comprising the step of: delivering into the subject a molecule having an IL13-moiety and a cytotoxic moiety in an amount effective to reduce the rate of growth of the glioma cells.

18. (Amended) A method of killing a glioma cell in situ, the method comprising the steps of:

(a) providing a mammalian subject having a cranium containing a glioma cell [, the glioma cell comprising an IL13-specific receptor that specifically binds IL13 with a greater affinity than it binds IL4];

(b) providing a molecule having an IL13-moiety and a cytotoxic moiety; and

(c) contacting the glioma cell contained within the cranium of the mammalian subject with the molecule in an amount effective to kill the glioma cell.

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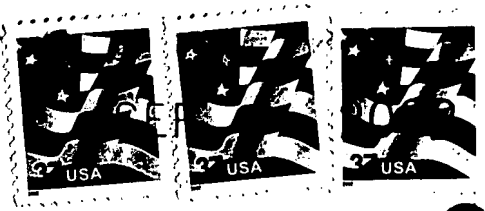

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